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TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
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USAEHA-51-0817-77

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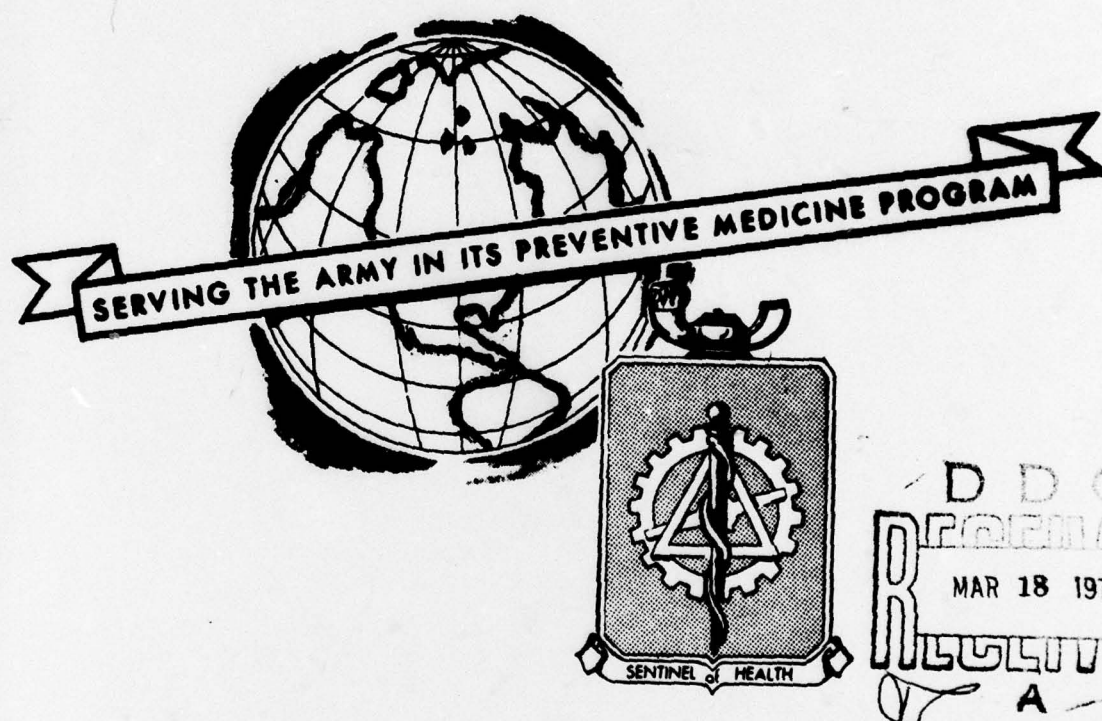
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TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENT AI3-36540-a
1-(CYCLOHEXYLCARBONYL)-2,6-DIMETHYLPYPERIDINE
STUDY NUMBER 51-0817-77
OCTOBER 1975 - DECEMBER 1976

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US ARMY
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ABERDEEN PROVING GROUND, MD 21010

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A hazard evaluation of AI3-36540-a was conducted using New Zealand White rabbits for skin and eye studies; Hartley guinea pigs for a skin sensitization study; and Sprague-Dawley, Wistar-derived rats for determination of acute oral toxicity. AI3-36540-a is a potential sensitizing chemical. Technical grade compound produced severe injury to the cornea and to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man. Ethanol solutions of this compound caused a photochemical skin irritation reaction in rabbits and may prove to be phototoxic on the skin of man.			

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Based on these findings it is recommended that AI3-36540-a not be approved for further testing as a candidate insect repellent.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
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11 MAR 1977

TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE, INSECT REPELLENT AI3-36540-a
1-(CYCLOHEXYLCARBONYL)-2,6-DIMETHYLPYPERIDINE
STUDY NUMBER 51-0817-77
OCTOBER 1975 - DECEMBER 1976

ABSTRACT

A hazard evaluation of AI3-36540-a was conducted using New Zealand White rabbits for skin and eye studies; Hartley guinea pigs for a skin sensitization study and Sprague-Dawley Wistar-derived rats for determination of acute oral toxicity. AI3-36540-a is a potential sensitizing chemical. Technical grade compound produced severe injury to the cornea and to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man. Ethanol solutions of this compound caused a photochemical skin irritation reaction in rabbits and may prove to be phototoxic on the skin of man. Based on these findings it is recommended that AI3-36540-a not be approved for further testing as a candidate insect repellent.

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DEPARTMENT OF THE ARMY
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TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENT AI3-36540-a
1-(CYCLOHEXYLCARBONYL)-2,6-DIMETHYLPYPERIDINE
STUDY NUMBER 51-0817-77
OCTOBER 1975 - DECEMBER 1976

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, FL, 17 October 1975.

b. Memorandum of Understanding Between the US Department of the Army, Office of The Surgeon General, the US Army Health Services Command, The US Army Environmental Hygiene Agency, the Armed Forces Pest Control Board and the US Department of Agriculture, effective December 1970 with Amendment No. 1, effective August 1974.

2. REFERENCE. Toxicology Division Procedural Guide, USAEHA, 1972.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellent AI3-36540-a.

4. SUMMARY OF FINDINGS. A hazard evaluation of the candidate repellent AI3-36540-a[1-(cyclohexylcarbonyl)-2,6-dimethylpyperidine] was conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study and Sprague-Dawley Wistar-derived rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:*

* The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," (1972) as prepared by the Committee on Revision of the "Guide for Laboratory Animal Facilities and Care," of the Institute of Laboratory Animal Resources, National Research Council (1972). The experiments reported herein were performed in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Study No. 51-0817-77, Oct 75 - Dec 76

Test	Results	Interpretation
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Compound AI3-36540-a produced mild primary irritation of the intact skin and of the skin surrounding an abrasion.	USAEHA Catagory II (ref Appendix)
0.5 ml technical grade compound applied to each of six rabbits.		
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 ml technical grade compound to one eye of each of six New Zealand White rabbits.	Compound AI3-36540-a produced moderate injury to the cornea and, in addition, some injury to the conjunctiva. No signs at seven days.	USAEHA Category E (ref Appendix)
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u>		
Rats (male) - corn oil diluent.	ALD >4900 mg/kg Dosages 3300 mg/kg and higher produced nasal discharge and ruffled pelt.	Presents little lethal hazard from acute accidental ingestion.

Test	Results	Interpretation
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
A single application (0.05 ml) of a 25 percent (w/v) solution of AI3-36540-a and of a 10 percent (w/v) oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six New Zealand White rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes from a distance of 10 - 15 cm.	A 25 percent solution of AI3-36540-a in ethanol applied to the unoccluded skin of rabbits caused on the UV irradiated areas very slight to well defined erythema and edema in six out of six rabbits for up to two days after administration and on the unirradiated skin areas only very slight erythema in six out of six rabbits.	Compound AI3-36540-a demonstrated potential for causing increased skin irritation following UV irradiation and may cause a photochemical skin reaction in man.
Application area were checked for irritation at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated areas.	
<u>Control</u>		
Following UV exposure of the rabbits, 0.05 ml of test compound, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites.		
Application areas were checked for irritation at 24, 48 and 72 hours.		

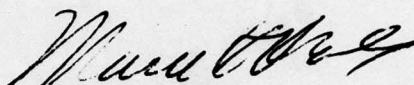
Test	Results	Interpretation
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injection of 0.1 ml of a 0.1 percent suspension (w/v) of AI3-36540-a or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs received and challenged with a 0.1 percent solution of AI3-36540-a.	Challenge dose of test compound (last intradermal injection) produced a sensitization reaction in eight of ten guinea pigs.	Compound AI3-36540-a is considered a potential sensitizing compound and is expected to produce a sensitization reaction in man.
Ten positive control guinea pigs received and challenged with 0.1 percent suspension of DNCB.	Positive control (DNCB) produced a marked sensitization reaction in ten out of ten guinea pigs.	
Ten cage control guinea pigs	Cage control guinea pigs showed no greater reaction to test compound and DNCB than were seen in original test groups.	
Five received challenge dose of test compound without prior sensitizing dose.		
Five received challenge dose of DNCB without prior sensitizing dose.		

* A known skin sensitizer

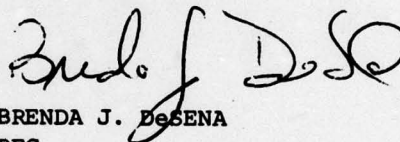
Study No. 51-0817-77, Oct 75 - Dec 76

5. CONCLUSIONS. AI3-36540-a is a potential sensitizing chemical. Technical grade compound produced severe injury to the cornea and to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man. Ethanol solutions of this compound caused a photochemical skin irritation reaction in rabbits and may prove to be phototoxic on the skin of man.

6. RECOMMENDATIONS. Under the provisions of Memorandum of Understanding (reference paragraph 1b), it is recommended that AI3-36540-a, 1-(cyclohexylcarbonyl)-2,6-dimethylpiperidine not be approved for further testing as a candidate insect repellent.

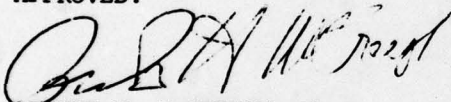


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APPENDIX

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals. prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.